DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug
Administration
Rockville MD 20857

NDA 18-081/S-038
NDA 18-082/S-024
NDA 18-723/S-029
NDA 19-680/S-015
NDA 20-593/S-009
NDA 21-168/S-003

Abbott Laboratories
Pharmaceutical Products Division
Attention: Lee M. Muraoka, BSPharm, MS
Senior Regulatory Affairs Specialist
200 Abbott Park Road
D-491/AP30-1E
Abbott Park, IL 60064-6157

Dear Mr. Muraoka:

Please refer to your supplemental new drug applications dated June 12, 2002, received June 13, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Depakene Capsules, Depakene Syrup, Depakote Tablets, Depakote Sprinkle Capsules, and Depakote ER Tablets.

Please also refer to your supplemental new drug application dated June 27, 2002, received June 28, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Depacon Injection.

These "Changes Being Effected" supplemental new drug applications provide for additions to the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the package insert regarding hyperammonemic encephalopathy in patients receiving valproate therapy, particularly as it relates to patients with known urea cycle disorders (UCD).

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package insert submitted June 12, 2002 for NDA 18-081/S-038, NDA 18-082/S-024, NDA 18-723/S-029, NDA 19-680/S-015 and NDA 21-168/S-003; package insert submitted June 27, 2002 for NDA 20-593/S-009; patient package insert submitted June 12, 2002 for NDA 18-723/S-029). Accordingly, these supplemental applications are approved effective on the date of this letter.

In addition, we note that, in two separate correspondences (dated December 2, 2002 and December 6, 2002), we requested additional revisions to the valproate labeling regarding hyperammonemic encephalopathy. In a December 11, 2002 correspondence to Dr. Ware of this Division, Abbott agreed to make the requested revisions to the package inserts for the above valproate products and to implement these revisions at the next printing (but no later than December 31, 2003) of labeling. Specifically, Abbott agreed to:

1. Under the **WARNINGS/Urea Cycle Disorders (UCD)** section, restate the sentence (from the "CONTRAINDICATIONS" section), regarding patients with know UDC, at the beginning of this section, and add a cross-reference to the **CONTRAINDICATIONS** section to the parenthetical phrase at the end of the last sentence in the paragraph. Specifically, the section would read as follows:

   "Urea Cycle Disorders (UCD)
   Divalproex sodium is contraindicated in patients with known urea cycle disorders.
   Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of valproate therapy, evaluation for UCD should be considered in the following patients: 1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; 3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); 4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders (see **CONTRAINDICATIONS** and **PRECAUTIONS**)."

2. Under the **PRECAUTIONS/Hyperammonemia** section, add a cross-reference to the **CONTRAINDICATIONS** section to the parenthetical phrase at the end of the last sentence in the 1st paragraph . Specifically, the sentence would read "Appropriate interventions for treatment...underlying urea cycle disorders (see **CONTRAINDICATIONS** and **WARNINGS-Urea Cycle Disorders**)."

Please also note that, in the Depakote Capsules labeling (NDA 18-723/S-029), there is a grammatical error in the sentence under the "Other Patient Populations, Dermatologic" subsection of the ADVERSE REACTIONS section. Specifically, you have added the word "had" to the following sentence, and it reads "An additional case of toxic epidermal necrosis resulting in death was reported in a 35 year old patient with AIDS taking several concomitant medications and had with a history of multiple cutaneous drug reactions." We ask that you correct this error, by deleting the word "had", at the next printing of this labeling.

Lastly, we note that, on June 14, 2002, a letter communicating information about reports of hyperammonemic encephalopathy in patients with urea cycle disorders using these drug products (i.e., a "Dear Health Care Professional" letter) was issued to physicians and others responsible for patient care.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Project Manager, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz

12/12/02 10:04:56 AM